IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: ARMODAFINIL PATENT LITIGATION	MDL Docket No. 1:10-md-2200-GMS
CEPHALON INC. and CEPHALON FRANCE, Plaintiffs, v. WATSON LABORATORIES, INC., Defendant.	Civil Action No. 1:10-cv-7-GMS
CEPHALON INC. and CEPHALON FRANCE, Plaintiffs, v. SANDOZ INC., Defendant.	Civil Action No. 1:10-cv-55-GMS Civil Action No. 1:11-cv-782-GMS
CEPHALON INC. and CEPHALON FRANCE, Plaintiffs, v. LUPIN LIMITED, Defendant.	Civil Action No. 1:10-cv-210-GMS
CEPHALON INC. and CEPHALON FRANCE, Plaintiffs, v. APOTEX INC., Defendant.	Civil Action No. 1:10-cv-695-GMS Civil Action No. 1:10-cv-1078-GMS

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

Further to the bench trial in this matter held July 17-20, 2012, and pursuant to the Stipulation Regarding Post-Trial Briefing filed September 13, 2012 [DI 303], and entered on September 25, 2012 [DI 311], Cephalon, through its undersigned counsel, hereby presents its post-trial proposed findings of fact and conclusions of law.

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CITATION FORMS, ABBREVIATIONS, AND WITNESS TESTIMONY

Explanation of Citation Forms

DI	Docket Index for Case No. 1:10-md-2200
FOF	A paragraph in Cephalon's Proposed Findings of Fact
PO	Proposed Joint Pretrial Order filed March 30, 2012 [DI 259] (so ordered, June 25, 2012)
Tr.	Citation to trial transcript (Tr. omitted if witness name is provided)
UF	A paragraph in the parties' statement of uncontested facts [PO Exhibit A]

Abbreviations

'290 Patent	U.S. Patent No. 4,177,290 [JTX-90]
'570 Patent	U.S. Patent No. 7,132,570 B2 [JTX-001]
'855 Patent	U.S. Patent No. 4,927,855 [JTX-103]
'918 Application	U.S. Patent Application No. 10/539,918 [JTX-002]
ANDA	Abbreviated New Drug Application
API	Active pharmaceutical ingredient
Apotex	Defendant Apotex Inc.
Cephalon	collectively, Plaintiffs Cephalon Inc. and Cephalon France
Defendants	collectively, Apotex, Lupin, Sandoz, and Watson
DSC	Differential scanning calorimetry
FDA	U.S. Food and Drug Administration
NDA	New drug application
Lupin	Defendant Lupin Limited
Orange Book	The FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations"
PTO	U.S. Patent and Trademark Office
Sandoz	Defendant Sandoz Inc.
Watson	Defendant Watson Laboratories Inc.
XRPD	X-ray pattern diffraction

Citations to Live Trial Testimony

Bernstein	Cephalon's expert Dr. Joel Bernstein (Trial Day 3, p. 482-631)
Cima	Defendants' expert Dr. Michael J. Cima (Trial Day 2, p. 371-470)
Hollingsworth	Defendants' expert Dr. Mark Hollingsworth (Trial Days 1-2, p. 60-270)
Lee	Defendants' expert Dr. Albert Lee (Trial Day 2, p. 271-343)
Mallamo	Cephalon's fact witness Dr. John Mallamo (Trial Days 3-4, p. 632-706)
Myerson	Cephalon's expert Dr. Allan S. Myerson (Trial Day 4, p. 723-789)
Robie	Defendants' expert Dr. Stephen Robie (Trial Day 2, p. 345-369)
Selbo	Cephalon's expert Dr. Jon G. Selbo (Trial Day 4, p. 708-722)

Citations to Deposition Trial Testimony

Blomsma	Cephalon's witness Dr. Erwin Blomsma (p. 818-825)
Coquerel	Cephalon's witness Gerard Coquerel (p. 828-843)
Leproust	Cephalon's witness Pierre Leproust (p. 802-818)
Serrure	Cephalon's witness Giles Serrure (p. 843-857)
Neckebrock	Cephalon's witness Oliver Neckebrock (p. 870-880)

BACKGROUND TO THE SCIENCE, THE '570 PATENT, AND THIS DISPUTE

[001] This is an ANDA patent infringement case regarding the '570 Patent. Asserted claims 6 and 9 recite "pharmaceutical compositions" "consisting essentially of" a specific solid state crystalline form, or "polymorph," of armodafinil known as Form I. Defendants stipulated to infringement, but argued that the asserted claims are inherently anticipated by and obvious over the '855 Patent, which discloses how to make "white crystals" of armodafinil in an experiment called "Preparation I." Defendants, however, have not met their burden to show invalidity by clear and convincing evidence.

[002] Cephalon cited the '855 Patent to the PTO during prosecution of the '570 Patent. The PTO found claims 6 and 9 neither anticipated by nor obvious over the '855 Patent in view of arguments and declarations submitted by Cephalon with experimental evidence showing that the final step of Preparation I—a "recrystallization from ethanol"—did not necessarily and inevitably produce Form I armodafinil, and that Form I was not obvious. At trial, Defendants attempted to distinguish that evidence by relying upon their experts' alleged complete reproductions of Preparation I and testimony as to obviousness; however, these experiments were flawed and incomplete, and in fact prove that claims 6 and 9 are neither anticipated nor obvious. Defendants' evidence cannot overcome the presumption of validity and the PTO's assessment of patentability over the '855 Patent should stand.

[003] In order to show inherent anticipation of the "pharmaceutical compositions" "consisting essentially of" Form I armodafinil, Defendants needed to prove that Form I armodafinil—with no other active ingredients, including no other polymorphs of armodafinil, and optionally only with other ingredients acceptable for pharmaceutical use—was the necessary and inevitable result of practicing Preparation I. However, Defendants' experts did not accurately and adequately practice Preparation I. They failed to follow the procedure as written

or consider a range of variables that would have been reasonable to skilled artisans, all of which could have affected the form of the final product. In fact, one of Defendants' experts, Dr. Lee, admitted that Defendants' counsel told him to use particular experimental conditions that had been shown to lead to the formation of Form I. Even more significantly, Defendants' experts obtained products that did not consist of Form I with pharmaceutically acceptable ingredients, as they contained other armodafinil forms and unknown amounts of additional impurities. Defendants' experiments are thus insufficient to meet their high burden to prove invalidity.

[004] As to obviousness, Defendants relied solely upon the '855 Patent and expert testimony regarding the level of skill in the art. Their arguments are inconsistent with the unpredictability of polymorphism, which was widely recognized in the publications from the relevant time period and reinforced by Defendants' experiments in this case. Cephalon's expert, Professor Joel Bernstein, explained that a skilled artisan could not have predicted, or even have had a reasonable expectation, that (1) armodafinil would exhibit polymorphism, (2) that a solid form with the structure of Form I even existed, or (3) what experimental conditions were needed to make Form I. The evidence, in conjunction with a proper interpretation of the law, supports the non-obviousness of the asserted claims, just as the PTO found after assessing the '855 Patent.

[005] Accordingly, Defendants have not proven that asserted claims 6 and 9 of the '570 Patent are either inherently anticipated by or would have been obvious over the '855 Patent. Cephalon asks that the Court enter judgment upholding the validity of the '570 Patent.

I. Cephalon's Unexpected Discovery That Armodafinil Exhibits Polymorphism Led to the '570 Patent

[006] Armodafinil, (-)-2-[(R)-(diphenylbenzhydrylsulphinyl)]acetamide, is also known as CRL 40982, (-)-modafinil, or the R-enantiomer of modafinil. [UF 36-38.] The molecule is enantiomeric, meaning that it can have different, non-superimposable three-dimensional spatial

arrangements. [UF 39.] S-modafinil is the mirror image enantiomer of armodafinil, and the two enantiomers have different optical and biological properties. [UF 40; JTX-103-2 at 1:67-2:2, -3 at 3:56 & 4:10.] Modafinil is a racemic mixture containing equal amounts of both the R-enantiomer and the S-enantiomer of modafinil. [UF 38.]

[007] Many organic compounds, including active pharmaceutical ingredients ("APIs") used in drug products, exist as solids, and some exist in more than one solid state form. [*See* JTX-32-2.] For example, some compounds can be formed into multiple, different crystal structures—a phenomenon known as "polymorphism."[1] [*See* JTX-26-3,-4; JTX-23-2; Bernstein 499:2-18 (PDX-1-6).] Some solid compounds also may be crystalline solvates, meaning that their crystal structure is uniquely based on the inclusion of both the compound and a solvent. [Bernstein 526:4-15.] The terms "crystallization" or "recrystallization" refer to a process whereby a molecule in solution undergoes a change in phase that results in the formation of a solid. [*See* JTX-56-3.] For a compound that exhibits polymorphism or forms solvates, different conditions of crystallization can yield different polymorphs. [*See*, *e.g.*, JTX-27-12 to 14.] Due to unpredictability in the process, even crystallizations under seemingly identical conditions might yield different crystal forms. [Bernstein 583:19-585:19; Blomsma 823:7-22.]

[008] Armodafinil is not a naturally occurring compound and was invented by Cephalon. [*See* JTX-103-5 at 7:19.] The '855 Patent is directed to that new molecule [*see* JTX-103-1 at Abstract; Hollingsworth 156:9-18], and Preparation I discloses how to synthesize it [JTX-103-3 at 3:5-56; Mallamo 674:7-9; Hollingsworth 95:12-14, 157:8-13; Lee 307:12-15]. Polymorphs of man-made compounds, such as armodafinil, must be synthesized by human

[1] Solid forms of polymorphs may exist with different chemical compositions such as salts, hydrates, solvates, and co-crystals. [*See* Cima 373:19-374:1.] Some compounds may also exist as amorphous solids, meaning that unlike a crystal they lack long range order, or a repeatable atomic arrangement. [Bernstein 528:1-15; Selbo 714:3-6.]

effort; they do not exist in nature. [*See* Bernstein 503:4-9.]

[009] In May 2000, Cephalon employee Olivier Neckebrock performed a series of recrystallization experiments that determined, for the first time, that armodafinil exhibits polymorphism. [Mallamo 636:3-638:4, 644:16-645:10; Neckebrock 874:10-875:13, 879:5-21; PTX-135-4; Serrure 850:9-12.] His experiments revealed two crystal forms, designated Form I (Type 1 or α) and Form II (Type 2 or β).[2] [PTX-572-19.] Later experiments yielded more forms and solvates. [*See* JTX-1-21 to 22 at 6:63-7:61.]

[010] Because they have different structures, polymorphs typically exhibit different properties, and armodafinil is no exception. [Bernstein 516:22-519:23 (JTX-26-9); JTX-45-5.] Armodafinil polymorphs may be characterized and differentiated by a variety of analytical techniques. [*See* PTX-585-51.] The technique of x-ray powder diffraction (XRPD) detects the intensity of x-rays reflected off of a sample that is rotated through various angles and produces a pattern, or fingerprint, that is unique to a particular crystal form. [*See* PTX-585-60; Bernstein 607:23-608:1.] XRPD directly represents the physical dimensions, *i.e.*, the interplanar spacings, within the crystal structure. [Bernstein 505:20-507:7 (PDX-1-13).] Melting points can also distinguish one polymorph from another. [*See*, *e.g.*, JTX-26-30 to 31; Mallamo 658:13-662:24 (JTX-120-5 to 7, 22).]

[011] In June 2005, Cephalon filed the '918 Application with the PTO, claiming priority to a French application filed in December 2002.[3] [*See* JTX-2-2.] The application describes five different polymorphic forms of armodafinil (Forms I to V), as well as two solvates of armodafinil. [*See* JTX-2-12 to 14.] Detailed XRPD fingerprint information for Form I is also

[2] Earlier, in August 1989, Cephalon employee Pierre Leproust had synthesized a solid state form of armodafinil that, as a result of Mr. Neckebrock's experiments, was eventually identified as Form I. [Mallamo 645:11-25; Leproust 803:16-804:16; PTX-132-10 (Ref. 5/2502); PTX-392.]

[3] Based upon the work of Mr. Leproust and Mr. Neckebrock, and the priority date of the French application, the date of invention for the claims of the '570 Patent is prior to December 20, 2001.

provided, including interplanar spacings, reflection values, relative intensities, and the results of single crystal x-ray analysis. [*See, e.g.*, JTX-1-19 to 20 at 2:48-3:10, -38 at 40:1-10.]

[012] Cephalon later filed an Amendment that provided claims directed to the armodafinil Form I polymorph. [JTX-71-2 to 3.] Cephalon also submitted an Information Disclosure Statement that cited the '855 Patent [JTX-2-1045], declarations from Drs. Erwin Blomsma, John Mallamo, and Matthew Peterson [JTX-38] with the results of armodafinil recrystallization experiments in the solvent (ethanol) disclosed in the '855 Patent, and an extensive discussion of why the '855 Patent did not inherently anticipate or render obvious the Form I armodafinil claims. [JTX-71-7 to 13.] This information showed that the form of armodafinil produced from a "recrystallization from ethanol" depends upon the conditions used, and that it was not necessarily and inevitably Form I. [JTX-71-9 to 12.]

[013] The PTO rejected the pending Form I armodafinil claims as either anticipated by or obvious in part over the '855 Patent. [*See* JTX-2-1412 to 1414.] After Cephalon responded [JTX-2-1431 to 39], the PTO withdrew the rejections, (1) acknowledging that the '855 Patent "is silent regarding the conditions that were used to perform the recrystallization," (2) noting that "Applicants have established by way of declarative evidence that recrystallization of [armodafinil] from ethanol, as taught by the Lafon '855 Patent, leads to the production of various polymorphic forms of the compound, depending upon the particular conditions employed to perform the recrystallization," and (3) concluding that "it cannot be said that practicing the teachings of the Lafon patent would necessarily result in a polymorphic form of [armodafinil] as recited in the instant claims." [PTX-122-2 to 3; Myerson 757:22-759:11.]

II. Defendants' ANDAs to Nuvigil® Resulted in this Litigation

[014] After discovering the numerous polymorphic forms of armodafinil, Cephalon developed an armodafinil drug product consisting essentially of Form I. [Mallamo 640:4-13.]

Today, Cephalon holds NDA No. 21-875 for armodafinil tablets, which it sells in the United States under the trade name Nuvigil®. [UF 9, 10.] Nuvigil® is an effective, once-daily medication approved by FDA for the treatment of various sleep disorders, and in particular is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, narcolepsy, and shift work disorder. [UF 11; PTX-4.] Polymorphic form I was chosen for Nuvigil® for its favorable aggregate of properties, including solubility and stability. [Mallamo 639:12-18, 641:1-23, 676:10-18.]

[015] The '570 Patent is listed in the Orange Book for Nuvigil®. [UF 12.] Cephalon owns and has the right to sue for infringement of the '570 Patent. [PO at ¶ 40-43; DI 258 at ¶ 3.] Defendants submitted ANDA Nos. 200-156 (Watson), 200-511 (Sandoz), 200-751 (Lupin), and 20-1514 (Apotex) to obtain FDA approval to sell generic armodafinil products prior to the expiration of the '570 Patent, which prompted this lawsuit. [UF 16, 18, 21, 25, 26, 28, 31.]

[016] The Court held a four-day bench trial on July 17-20, 2012. The only issues to be decided by the Court are Defendants' allegations of inherent anticipation and obviousness.[4]

III. Only "Pharmaceutical Composition" Claims "Consisting Essentially of" Form I Armodafinil Are at Issue

[017] Cephalon has asserted claim 6 (as it depends upon claim 2) and claim 9 of the '570 Patent. [DI 295.] The Court has construed the terms of these claims. [*See* DI 172.]

[018] Claim 6 recites: "A pharmaceutical composition consisting essentially of a

[4] Defendants had alleged that certain claims of the '570 Patent lacked written description, but did not include that defense as an issue for trial in the Pretrial Order, which excludes it from the case. [*See* Pretrial Conf. (June 25, 2012) Tr. at 42:13-15.] After trial, in email correspondence dated July 27, 2012, counsel for Watson confirmed on behalf of all Defendants that "Defendants are no longer asserting lack of inventorship as a defense to the '570 patent-in-suit." Accordingly, those issues are not before the Court and Cephalon has not addressed them in this paper.

laevorotatory enantiomer of modafinil according to[5] any one of claims 1 to 4." [JTX-1-38 at 40:34-36.] As dependent upon claim 2 and as construed by the Court, claim 6 recites a composition consisting of the specified pharmaceutically active component—a laevorotatory enantiomer of modafinil in a polymorphic form that produces a powder X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02, 3.98 (Å), and further comprising intensity peaks at the interplanar spacings: 13.40, 6.34, 5.01, 4.68, 4.62, 4.44, 4.20, 4.15, 3.90, 3.80, 3.43 (Å)—and optionally unlisted pharmaceutically acceptable ingredients that do not materially affect the basic and novel properties of the specified pharmaceutically active component. [*See* DI 172.]

[019] Claim 9 recites: "A pharmaceutical composition consisting essentially of a Form I polymorph of (-)-modafinil according to claim 7." [JTX-1-38 at 40:40-41.] As construed by the Court, claim 9 recites a composition consisting of the specified pharmaceutically active component—a crystal form of armodafinil distinguishable as Form I—and optionally unlisted pharmaceutically acceptable ingredients that do not materially affect the basic and novel properties of the specified pharmaceutically active component. [*See* DI 172.]

[020] Taken together, the constructions of claims 6 and 9 specify pharmaceutical compositions with an active component "consisting of" Form I armodafinil, meaning that Form I must be the only crystal form of armodafinil present in the compositions, and that any additional ingredients be pharmaceutically acceptable. [Hollingsworth 256:5-14; Myerson 756:6-16.] Unasserted claims 5 and 8 of the '570 Patent recite a composition "comprising" Form I armodafinil, which would allow for other active ingredients and forms of armodafinil. [JTX-1-38 at 40:33-35 & 40:38-39; *see* DI 172.]

[5] A Certificate of Correction dated July 10, 2007, and attached to the '570 Patent, deletes the second occurrence of "according to" that appears in the original printing of claim 6. [JTX-1-40.]

DEFENDANTS ADMITTED TO INFRINGEMENT OF CLAIMS 6 AND 9

[021] Defendants have stipulated to, and thus conceded, infringement of the asserted claims as construed by the Court. [PO at ¶ 40-43; DI 258 at ¶ 3.] Thus, no findings of fact or conclusions of law as to Defendants' infringement of claims 6 and 9 are needed.

INHERENT ANTICIPATION HAS NOT BEEN PROVEN

[022] Defendants allege that claims 6 and 9 of the '570 Patent are inherently anticipated by the '855 Patent based on experiments conducted by their experts. However, as required by the relevant law and consistent with the evidence presented in Cephalon's PTO declarations, that testing did not show Preparation I to necessarily and inevitably produce a pharmaceutical composition consisting of Form I armodafinil and other pharmaceutically acceptable ingredients. Instead, Defendants' testing showed that mixtures of polymorphic forms and various uncharacterized impurities may result. Their testing is also flawed and insufficient because it departed from the express method taught in the '855 Patent and is not representative of its full scope. Therefore, Defendants have not proven inherent anticipation.[6]

IV. Findings of Fact Related to Inherent Anticipation

A. The '855 Patent Does Not Disclose or Teach Form I Armodafinil

[023] Defendants' and Cephalon's witnesses agree that the '855 Patent neither mentions nor describes polymorphism, much less any polymorphic form of armodafinil.[7]

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[6] Dr. Hollingsworth also testified that the'570 Patent discloses that if one follows the recrystallization from methanol protocol disclosed in the '290 Patent, one would obtain Form I armodafinil. [89:25-90:7.] But none of Defendants' experts cited any authority or performed any experiments to demonstrate that Form I was the necessary and inevitable from such a procedure. Furthermore, as Dr. Mallamo explained both to the PTO and this Court, the statement in the '570 Patent that the '290 Patent leads to Form I armodafinil is erroneous. [Mallamo 688:15-689:11 (JTX-120-1 to 2 at ¶ 4).]

[7] On the FDA patent listing form asking if the '855 Patent "claim[s] a drug substance that is a different polymorph" of armodafinil than in Nuvigil®, Cephalon appropriately answered "no" because the '855 Patent does not disclose or claim any polymorphs. [JTX-130-2.] On the form

[Hollingsworth 157:5-7, 234:9-17; Lee 307:8-11; Bernstein 537:3-6, 630:8-12; Mallamo 648:6-8; 653:18-654:4.] Preparation I also does not disclose the crystallization conditions needed to make any particular polymorph, such as the solvent, the cooling rate, and the concentration, all of which can affect the result. [Hollingsworth 157:14-158:11; Bernstein 564:19-566:19; JTX-7-3 Tbl. 1; Myerson 745:3-7, 750:10-12, 764:2-7.] The "white crystals" of Preparation I were characterized by an instantaneous melting point later found by Cephalon to be inconsistent with Form I. [JTX-103-3 at 3:55; Bernstein 563:13-22; Mallamo 683:22-684:11 (JTX-120-19), 699:7-701:2.] On that basis alone, the '855 Patent does not inherently anticipate the asserted claims.

B. Preparation I of the '855 Patent Does Not Inherently Produce Form I Armodafinil or a Composition Consisting Essentially Thereof

[024] The testing evidence presented at trial showed that Preparation I and a "recrystallization from ethanol" do not inherently produce Form I armodafinil or a composition consisting essentially thereof. Instead, they can yield different forms, mixtures of forms, and unknown impurities, evidently depending on numerous variables not specified in the '855 Patent.

1. Defendants' Experimental Evidence Presented at Trial Yielded Mixtures of Forms and Contained Impurities

[025] Defendants' expert Dr. Hollingsworth performed two experiments, Run 1/2 and Run 3/4, which he described as based on Preparation I [91:2-4], and performed XRPD testing on the armodafinil he generated [106:3-7]. Run 1/2 produced Form I armodafinil. [106:8-19; Myerson 748:25-749:19 (PDX-5-14).] Run 3/4 after a first recrystallization from ethanol produced Form I accompanied by some other unknown crystalline impurities, and after a second recrystallization from ethanol produced a mixture of Forms I and II. [195:16-200:7 (CDX-1 to

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for the '570 Patent, Cephalon answered that question "no" for a different reason: the '570 Patent does not claim a different polymorph than used in Nuvigil®—it claims Form I. [JTX-132-2.]

4); 249:23-251:13[8] (CDX-5, CDX-6); Myerson 748:25-749:19 (PDX-5-14.]

[026] Dr. Hollingsworth also performed XRPD testing on intermediate samples that were produced at two intermediate points along step (d): after the methanol evaporation and after the ether wash. He concluded that both samples contained Form I. [114:23-117:17.] Cephalon's experts Drs. Smith and Selbo performed a synthesis of armodafinil up to the same points in step (d)— using different, but reasonable, experimental conditions—and found their products to be amorphous, non-crystalline forms. [Selbo 710:6-711:7, 713:20-716:19 (PTX-174, PTX-175).] Drs. Smith and Selbo thus demonstrated that the methanol evaporation and ether wash steps do not necessarily and inevitably produce Form I. [Selbo 716:14-19.]

[027] Defendants' expert Dr. Lee then attempted to reproduce Drs. Smith and Selbo's work,[9] also purporting to complete Preparation I through the final recrystallization step. [Lee 277:3-8, 309:18-25.] Dr. Robie analyzed Dr. Lee's samples by XRPD and concluded that they contain Form I with unknown impurities. [361:10-13, 361:23-362:12.] Defendants did not test Dr. Lee's intermediate products after the methanol evaporation and ether wash. [Lee 317:8-25.]

[028] Dr. Mallamo, Cephalon's vice-president of worldwide chemical research and development, discussed experimental results of armodafinil recrystallized from ethanol shown in the PTO declarations. [633:9-14, 644:16-645:10, 655:4-9, 657:11-16, 660:21-661:22.] These experiments showed that, depending on the conditions used, a "recrystallization in ethanol" does not necessarily produce Form I armodafinil.[10] [JTX-120-5 at ¶ 18.] Other testing showed that

[8] The transcript at 251:11 has a transcription error, referring to "methanol" instead of "ethanol."
[9] Dr. Lee admitted that he did not follow Drs. Smith and Selbo's procedure exactly. [292:6-11.]
[10] Dr. Hollingsworth opined that the PTO declarations are not valid. [129:19-131:7.] His comments on the Mallamo Declaration are predicated on an overly narrow interpretation of "ethanol." [FOF 55.] And his comments on the Peterson and Blomsma Declarations miss the point, which was to show that a wide variety of conditions for recrystallization from ethanol can result in multiple polymorphic forms, leading to a lack of predictability for Form I over the '855 Patent. [JTX-120-5 at ¶¶ 16-18.]

the instantaneous melting point of the product in the '855 Patent is inconsistent with Form I armodafinil. [JTX-120-6 at ¶ 20; *see also* Myerson 738:18-739:16]

2. Defendants' Testing Produced Mixtures of Armodafinil Forms, Thus a Composition "Consisting Essentially of" Form I Is Not Inherent

[029] It is known that "minor variations in preparative conditions can tip the balance in favour of crystallization of a polymorph which is not necessarily the thermodynamically stable one." [JTX-22-4.] While Dr. Hollingsworth asserts that statement to be true generally, but not for armodafinil [228:20-230:12], his work proves otherwise. While he contended that his Run 1/2 experiment produced "pure" Form I, his first recrystallization in Run 3/4 produced Form I and some other crystalline material. (249:23-251:24 (CDX-6), Myerson 745:15-746:12 (PDX5-8).] In his second Run 3/4 recrystallization, he used a slightly higher solute concentration of about 13.8%, and obtained a mixture that was mostly Form II armodafinil, instead of Form I that he obtained in other experiments using a 9.6% solution. [195:16-200:4 (CDX-1 to 4), 208:4-7 (CDX-1), 210:5-12; Myerson 748:25-749:19 (PDX-5-14).] Dr. Hollingsworth's formation of Form II and unknown crystals confirms that, as stated in the literature, small variations in procedure can yield very different polymorphic results. [Myerson 730:17-731:4; Bernstein 535:17-537:2.] Significantly, Dr. Hollingsworth admitted that his mixture of Forms I and II is not a composition containing only one pharmaceutically active form of armodafinil [253:15-254:12]; thus, it does not "consist[] essentially of" Form I armodafinil as required by asserted claims 6 and 9.[11] Indeed, mixtures of polymorphs have different properties than their individual constituents. [*See* Bernstein 523:10-525:2; PTX-585-129 Fig. 7.3.] These results prove that Form I would not be not inherent from Preparation I.

[11] As it is "specified" in claims 4 and 7, claims 6 and 9 require that Form I armodafinil be "the," as in only, pharmaceutically active component present in the claimed compositions. [*See* FOF 20; Hollingsworth 255:11-19, 256:12-14] Because Form II is pharmaceutically active [*see* JTX-1-24 at 12:5; JTX-12-10], its presence is excluded from claims 6 and 9.

3. Unidentified and Unquantified Impurities Show that Defendants' Experimental Products Are Not "Pharmaceutical Compositions"

[030] Asserted claims 6 and 9 recite a "pharmaceutical composition." However, the product of Preparation I is not suitable for pharmaceutical use, and Defendants' experts have not shown otherwise. [Bernstein 541:5-542:8; PTX-36-2 at ¶ 6; Myerson 756:11-16.] Dr. Cima acknowledged that one would need to prove that the amount and type of any impurities in an armodafinil product intended for human use are safe. [457:15-18, 459:1-11.] Yet Defendants' experts made no effort to determine the type or quantity of impurities in the samples from their experiments, or determine if they were pharmaceutically acceptable.[12] [Hollingsworth 251:9-24; Lee 339:1-16; Robie 365:24-366:18, 367:9-11.]

[031] Defendants' expert Dr. Cima and Cephalon's expert Dr. Bernstein agreed that the product of Preparation I will contain impurities, such as unreacted starting materials, reaction byproducts, or unreacted chemicals.[13] [Cima 457:19-458:2; Bernstein 540:20-541:1; *see also* Myerson 753:12-754:24 (PTX-123, PTX-127).] In fact, XRPD analysis of Dr. Hollingsworth's sample from Run 3/4 after the first ethanol recrystallization[14] showed the presence of three peaks that could not be attributed to the Form I fingerprint. [Hollingsworth 249:23-251:13 (CDX-6); PTX-411.] Dr. Hollingsworth believes those peaks to represent a chemical impurity, the amount

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[12] Defendants contend that the claimed pharmaceutical compositions can contain additional components, including impurities, that do not affect the basic and novel properties of Form I, and that different solid state forms of armodafinil and chemical impurities would not affect those properties. [*E.g.,* Hollingsworth 154:3-155:12]. But none of Defendants' experts tested any of the additional substances contained in their samples to determine whether they affected such properties. [FOF 31, 32.] Instead, the evidence shows that different solid state forms and/or impurities can affect the properties of Form I. [Bernstein 539:22-540:19 (JTX-27-21); Hollingsworth 163:22-25; Myerson 732:3-734:16 (PDX-5-13); Cima 465:7-467-1 (JTX-7-3).]

[13] Unlike Preparation I's reference to only one "recrystalliz[ation] from ethanol" [JTX-103-3 at 3:50], Cephalon's work routinely involved two recrystallizations in order to get a more pure product. [Myerson 740:9-742:7 (PTX-382-10,-11, Example 5/2502); *see also* JTX-120-19 (Example Nos. 5/2502, 1/0054(a), & 1/0920); JTX-120-20 (Example No. ON II/149 E).]

[14] The '855 Patent specifies only one recrystallization from ethanol. [JTX-1-3 at 3:50.]

or identity of which he failed to establish [251:9-24 (CDX-6); Myerson 746:7-12], preventing a conclusion that this product qualifies as a "pharmaceutical composition." Since at least one of their reproductions failed to yield a "pharmaceutical composition," their testing actually establishes that Preparation I does not inevitably result in a product that satisfies claims 6 and 9.

[032] Dr. Lee also did not test his experimental products, Samples 10 and 12S, for impurities [339:1-16], but instead sent them to Dr. Robie [305:5-6], who performed XRPD testing [Robie 361:10-13]. For Samples 10 and 12S there were five and nine XRPD peaks, respectively, revealing impurities that did not match to Form I armodafinil's fingerprint. [Robie 364:19-365:23 (PTX-587-1) (Sample 10); 363:21-364:18 (PTX-588-1) (Sample 12S).] Dr. Robie testified that he did not know the identity or the quantity of the impurities that account for those extra peaks [365:24-366:10], and that he did not perform any testing to identify or quantify the impurities [366:15-18]. Dr. Robie also admitted he did not know the effect that those impurities may have on the properties of Form I armodafinil. [366:11-14.] He testified that the samples may contain a mixture of Form I and some other armodafinil crystal forms [366:19-22], but he does not know the identity of those other forms, and in any event, is not an expert in polymorph identification [366:23-367:5]. Finally, Dr. Robie had no opinion on whether Samples 10 and 12S could be used in a pharmaceutical composition. [367:9-11.]

[033] Since the experiments of Defendants' experts, Drs. Hollingsworth, Lee, and Robie, contained unknown types and amounts of impurities such that they would not be a "pharmaceutical composition," Defendants have not shown that Preparation I necessarily and inevitably results in a product that satisfies the limitations of claims 6 and 9.

C. Defendants Did Not Prove That They Obtained the Same Product as Described in the '855 Patent

[034] Defendants have not proven that their experiments are even accurate

reproductions of Preparation I of the '855 Patent, which describes certain characteristics of the product, including yield and melting point. [JTX-103-3 at 3:51-56.]

1. Defendants' Experts Did Not Measure the Melting Point of Their Final Products Correctly

[035] Preparation I reports an instantaneous melting point ("M.p. (inst.)") of 153 to 154°C for the final armodafinil product. [JTX-103-3 at 3:55.] That test provides a way to confirm whether a particular substance is the same as the Preparation I product. [Myerson 737:6-11.] Defendants' experts did not measure instantaneous melting point for their products.

[036] The instantaneous melting point reported in Preparation I was measured using a "Kofler hot bar" device. [Mallamo 650:15-651:13; JTX-120-2 n.1.] The Kofler device comprises a metal bar across which an electrical current is applied to create a temperature gradient; the sample to be tested is sprinkled directly onto the bar so that the temperature at which the sample melts can be directly determined. [Mallamo 651:14-652:16 (PDX-4-1).] Determination of the instantaneous melting point is particularly important for compounds like armodafinil that degrade upon slow heating. [*See* FOF 40.]

[037] The instantaneous melting point reported in the '855 Patent suggests that the preparation does *not* result in Form I armodafinil. Dr. Mallamo provided information regarding the instantaneous melting points, measured using a Kofler hot bar, of various polymorphic forms of armodafinil. [JTX-120-5 to 6 at ¶¶ 19, 20; JTX-120-22; 658:16-659:17.] Form I armodafinil has an instantaneous melting point of 159°C or higher, while pure Form II armodafinil has an instantaneous melting point of 156°C. [JTX-120-22.] Instantaneous melting points of Form I/Form II mixtures ranged from 156°C to 160°C. [JTX-120-22.] None of the pure polymorphic forms or mixtures of polymorphic forms had instantaneous melting points approaching the 153-154°C data points reported for the product of Preparation I, and indeed the Preparation I product

had an instantaneous melting point closer to Form II than Form I.[15] On the basis of this information, Dr. Mallamo stated that "the data supports a conclusion that the [armodafinil] described in Preparation I of the Lafon '855 patent is NOT the claimed Form I [armodafinil]" of the '570 Patent. [JTX-120-6 at ¶ 20 (emphasis in original); Mallamo 700:1-701:2.] Dr. Myerson reviewed the information presented and agreed with that conclusion.[16] [738:18-739:16.]

[038] Defendants presented no evidence that Form I has an instantaneous melting point of 153-154°C, the range reported by Preparation I. In fact, Dr. Hollingsworth agreed that the instantaneous melting point reported in the '855 Patent does not appear to correspond to the instantaneous melting point reported for Form I [263:13-264:3], a conclusion with which Dr. Myerson agrees [743:12-744:5 (PDX-5-6), 773:23-774:10; 776:7-777:14].

[039] Neither Dr. Hollingsworth nor Dr. Lee used a Kofler hot bar to measure the instantaneous melting point of their samples. [Hollingsworth 185:12-21; Lee 303:16-18, 336:23-337:24; 328:7-9; Myerson 736:24-737:11.] Instead, they used capillary methods to determine melting point [Hollingsworth 192:8-18; Lee 337:2-4], which are different from the Kofler hot bar instantaneous method [Bernstein 564:10-14]. Those capillary methods involve a non-instantaneous, gradual heating of the sample, a measuring procedure that could take as long as 10-15 minutes. [Hollingsworth 192:24-193:4.] In addition, absolute values of melting points obtained using different instrumentation cannot be directly compared. [JTX-120-7 n.7.]

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[15] Because the instantaneous melting points of Form II and of mixtures involving Forms II and IV could be discretely measured [JTX-120-22], these data points also refute any suggestion by Dr. Hollingsworth that various polymorphic forms of armodafinil produced from Preparation I would have converted to Form I during testing on a Kofler hot bar [142:21-146:1.] In any event, Dr. Hollingsworth has never used or seen a Kofler hot bar [191:14-192:7], rendering suspect his opinion regarding polymorph conversion during such testing. Dr. Hollingsworth also admitted that any product that converted to Form I on the Kofler hot bar would not be a "pharmaceutical composition" [189:2-9], and thus it cannot meet the limitations of asserted claims 6 and 9.

[16] Dr. Myerson is an expert in the fields of crystallization, polymorphism, industrial applications of crystallization, and manufacturing of active pharmaceutical ingredients and final drug products. [Myerson 723:14-729:3.]

[040] The use of instantaneous melting point is particularly important for armodafinil. The Kofler hot bar "procedure is clearly rapid and is very useful for substances which tend to decompose upon gradual heating." [PTX-147-10.] Research at Cephalon confirms that non-instantaneous methods using slow heating rates, like differential scanning calorimetry, were not appropriate for armodafinil, which can degrade during these slower melting tests.[17] [JTX-111-1; Mallamo 659:18-660:14, 706:4-16; Myerson 737:12-738:13, 778:15-22.] This conclusion is consistent with data presented to the PTO, which shows that Form I can exhibit widely variant "melting points" (from 146.9 to 157°C) when measured by capillary melting point tests.[18] [JTX-120-7 n.7, -23; Mallamo 659:2-17.] Dr. Hollingsworth's melting point test exhibits exactly such a wide variability. [139:10-140:22.] Dr. Mallamo also stated that "absolute [melting point] values obtained using different instrumentation cannot be directly compared." [JTX-120-7 n.7.] Neither Dr. Hollingsworth nor Dr. Lee attempted to correlate or calibrate their melting points to the instantaneous melting point reported in the '855 Patent. [*See* Lee 337:7-24.]

2. Defendants' Yields Differed From the Yield of Preparation I

[041] The '855 Patent indicates that the "overall yield" for Preparation I—after completing all of steps (a) to (d)—is 32%. [JTX-103-3 at 3:51; Mallamo 649:21-650:3; Myerson 736:8-23.] With stated yields of 42% from step (a), about 100% from step (b), and 85% from step (c), step (d) must have a yield of about 90%. [Lee 332:3-17 (CDX2-6); Mallamo 650:4-14.] Dr. Mallamo testified that such a high yield is consistent with his experience. [650:4-14.]

[042] In his experiments, Dr. Hollingsworth had an overall yield of 8.2% for Run 1/2 and an overall yield of 9% for Run 3/4. [Myerson 735:3-9, 735:17-736:3 (PDX-5-3).] Dr.

[17] While Dr. Lee alleges that there was no decomposition of the samples, he did not actually observe any of the melting point determinations in his experiments. [327:17-328:9.]

[18] Because Dr. Lee only measured two different armodafinil samples using one method, he also cannot contradict the fact that Form I armodafinil can exhibit widely variant melting points using the capillary method. [336:21-337:4 (DDX-2-8); JTX-120-7 n.7, -23; Mallamo 659:2-17.]

Hollingsworth's yields are much lower than the 32% overall yield reported in Preparation I, and Dr. Myerson testified that such low yields are problematic. [729:16-730:16.]

[043] Dr. Lee had an overall yield of 7.4% for Run 1 (Sample 10) and an overall yield of 3.2% for Run 2 (Sample 12S). [Lee 333:12-20 (CDX2-8).] Dr. Lee acknowledged that the differences between the Preparation I yields and his yields were much greater than could be accounted for by reasonable experimental error. [329:3-14; 333:21-25.]

[044] In an attempt to justify their low yields, Drs. Hollingsworth and Lee testified that the "overall yield" of 32% reported in Preparation I actually refers to the step (d) yield, in which case the actual overall yield for Preparation I would be about 11%. [Hollingsworth 170:17-171:4; Lee 298:24-300:1.] To support their position, they point to the '570 Patent, which assigns 32% as the yield of step (d) [JTX-1-19 at 1:52], and compounds that error by assigning Preparation I a yield of 5.7% [JTX-1-19 at 2:9-13]. Dr. Mallamo acknowledged that the '570 Patent is incorrect in its characterization of yields from the '855 Patent.[19] [686:25-687:19; 689:23-690:12.] He further testified that a step (d) yield of only 32% would be inconsistent with Cephalon's actual experience of obtaining a very high yield using the step (d) chemistry. [650:4-14.] Other patent literature discussing the '855 Patent also accepts 32% as the overall yield for all of Preparation I, not just step (d). [PTX-124-3:1-11; PTX-123-3:1-14.]

[045] Differences in yield suggest different impurity profiles. [Myerson 735:17-736:7 (PDX-5-3).] This is important because "[t]he presence of impurities can have a profound effect on the growth of crystals" [JTX-27-21], as admitted by Dr. Hollingsworth [163:22-25, 227:11-23] and confirmed by Dr. Myerson in the context of Preparation I [732:3-734:16 (PDX-5-13)].

[19] Dr. Mallamo testified that he was not aware of this mistake in the '570 Patent when he submitted his declaration to the PTO. [689:12-14, 705:14-20.] In any event, mistakes in the '570 Patent regarding yield of the Preparation I method are irrelevant since they do not pertain to the Form I composition claims at issue. [*Cf.* Myerson 785:18-787:10.]

[*See also* Cima 465:7-467-1 (JTX-7-3).] Therefore, the results of Defendants' experiments, with vastly different yields than that of Preparation I, do not constitute reliable evidence of the solid state form of armodafinil that results from the '855 Patent.

D. Defendants' Experiments Were Flawed and Incomplete

[046] Defendants' inherency defense fails for another, independent reason. Defendants' experts failed to follow Preparation I as written or consider the range of variables that would have been reasonably available to skilled artisans. These defects could have affected the form of the final product, rendering the results insufficient to establish what is a necessary and inevitable result of practicing Preparation I.

1. Defendants' Experts Did Not Perform Preparation I as Written

[047] Step (b) of Preparation I of the '855 Patent states that "the (-)-benzhydrylsulfinylacetate of (-)-α-methylbenzylamine (17 g) obtained in this way is dissolved in 800 ml of warm water (30°-40° C.)." [JTX-103-3 at 3:22-24.] The '855 Patent also indicates elsewhere that this step should be performed at 30-45 °C. [JTX-103-2 at 2:31-32.] Dr. Hollingsworth and Dr. Lee admit that they did not perform Preparation I as written. Specifically, instead of using 30-40 °C, they both used much higher temperatures, e.g., 70°C and 90°C. [Hollingsworth 234:18-235:10; Lee 312:24-313:6.] Dr. Hollingsworth opined that dissolution at the stated 30-40 °C may be impossible [238:8-22], but had not fully tested his theory and conceded that the experiment forming the foundation for Preparation I could have used 30-40 °C [236:1-9]. Significantly, even using a melting point test method different from what is specified in the '855 Patent, Dr. Hollingsworth and the other experts obtained a product that had "a very wide range" of melting points inconsistent with the narrow melting point reported in the '855 Patent. [*See* FOF 39; Hollingsworth 237:18-238:7; Myerson 780:7-19.] Because they did not follow the stated procedure in step (b) and did not obtain the reported melting point, Defendants'

experiments cannot be considered to be probative of whether Preparation I would inherently or naturally result in Form I armodafinil.

2. Defendants Did Not Test a Representative Range of Conditions

[048] Preparation I has four major synthetic steps, labeled (a) to (d), but leaves open to the skilled artisan the selection of conditions used to carry out many of the listed steps. [JTX-103-3 at 3:5-56.] Instead of testing a variety of conditions that a skilled artisan might use to practice Preparation I, Defendants' experts chose only a narrow set of experimental conditions. Such narrow testing is legally insufficient to demonstrate inherency, as Defendants have the burden to demonstrate that all reasonable ways to practice Preparation I of the '855 Patent would necessarily result in a pharmaceutical composition consisting essentially of Form I armodafinil.

[049] More specifically, in step (a), the reaction time, reaction temperature, and recrystallization conditions are not specified; in step (b), the reaction time, filtration temperature, washing conditions, and drying conditions are not specified; and in step (c), the filtration conditions, washing conditions, and drying conditions are not specified. [Lee 307:25-308:4 (CDX2-1); Myerson 731:5-732:6 (PDX-5-1).] Further, step (d) of Preparation I leaves entirely open the specific experimental conditions for "recrystalliz[ation] from ethanol." [Bernstein 566:20-567:9; Mallamo 654:5-11; JTX-120-3 at ¶ 9; Coquerel 839:15-840:21.] It does not specify the form of the crude product to be recrystallized, the identity, and quantity of impurities in the crude product, the grade of ethanol, the amount of solvent, the starting temperature, the cooling rate, the final temperature, or the drying conditions. [Lee 308:5-19 (CDX2-2).] There are a vast variety of reasonable conditions that can be used for a crystallization, and the specific conditions of crystallization can affect the solid state form produced. [Bernstein 542:17-543:2; PTX-585-49; 564:19-21; JTX-120-5 at ¶¶ 17 & 18.]

[050] Thus, one would have to make many decisions, unsupported by the '855 Patent,

in order to practice Preparation I and skilled artisans could reasonably perform Preparation I in many different ways. [Myerson 731:5-732:6 (PDX-5-1); Lee 308:20-23.] Each choice among the possible options could impact the solid state form of the final product. [Hollingsworth 157:14-158:11; Bernstein 533:22-535:16 (JTX-22-4); 564:19-566-19 (JTX-7-3 Tbl. 1).] Depending on the choices made, the resulting product will contain different kinds and/or amounts of impurities, which can affect whether, and more importantly, which final solid state form (crystals, solvates, or amorphous compound) will result. [Myerson 732:7-23; *see also* 754:6-24 (JTX-127-3 & -5); Hollingsworth 163:22-25.] In particular, solvent composition, concentration, and cooling rate can impact the final solid state form. [Hollingsworth 226:20-227:10; JTX-27-13.] As discussed below, however, Defendants chose to limit their experiments by using only a narrow set of conditions for this step.

a. Defendants' Experts Unreasonably Limited the Concentration of Armodafinil Used In the Recrystallization Step

[051] The '855 Patent does not disclose the concentration of the armodafinil/ethanol solution used in the recrystallization of step (d), a parameter that can affect the final polymorphic form. [Hollingsworth 157:16-158:7, 226:20-227:7; JTX-27-13; Myerson 744:6-746:6 (PDX-5-7, 5-8).] By using only one concentration in all but one of their recrystallizations (which yielded a different result), the Defendants' testing fails to reasonably reflect the full scope of Preparation I.

[052] By way of background, standard textbooks indicate that a "MINIMUM AMOUNT(!)"of solvent, *i.e.*, a larger percentage (concentration) of solute, should be used for recrystallizations. [JTX-97-6; Myerson 746:13-748:5.] Cephalon's scientists routinely used a 20% concentration. [JTX-38-41 & -42 (Example Nos. 5/2502, 1/0054(a), 1/0920, and ON II/149E Step a); Hollingsworth 164:1-165:11.]

[053] Given the '855 Patent's failure to specify concentration for the recrystallization,

Dr. Hollingsworth admitted that skilled artisans might select a range of concentrations to use. [167:15-21; 168:15-20.] Despite this, he chiefly used only one concentration, 9.6%. [165:21-166:6, 178:14-22; Myerson 748:13-20 (PDX-5-15).] He, however, admitted that this concentration was not the minimum amount of solvent [170:8-16] taught by the prior art [JTX-97-6]. Notably, Dr. Hollingsworth had reviewed the '570 Patent and the PTO declarations prior to beginning his experiments, which provide that Form I is preferentially obtained using a low (*i.e.*, 7% or less) concentration solution. [159:1-3, 160:23-161:2, 165:12-20; JTX-1-32 at 27:37.] He also admitted that the 20% concentrations shown in the PTO declarations were reasonable. [167:9-14; JTX-38-41 & -42.] Instead of testing a different concentration or using his own independent judgment to determine the concentration(s) to use, Dr. Lee was instructed by counsel for Defendants to use the same 9.6% concentration shown by Dr. Hollingsworth to yield some amounts of Form I. [309:7-12, 319:16-320:5.]

[054] Tellingly, the one time Defendants' experts varied the solute concentration—using a 13.8% solution in the second recrystallization of Dr. Hollingsworth's Run 3/4—it produced a mixture of crystalline forms that was predominantly Form II armodafinil. [Hollingsworth 195:16-197:25, 207:12-208:7 (CDX-1).] This shows that reasonable variations in Preparation I yield different polymorphs of armodafinil, requiring a conclusion that Form I is not inherent in the teachings of the '855 Patent.

b. Defendants' Experts Used Only One Grade of Ethanol, Which Is Not Representative of the Scope of Preparation I

[055] Step (d) of Preparation I calls for "recrystalliz[ation] from ethanol" [JTX-103-3 at 3:50] without specifying a particular grade of ethanol. Ethanol is available in several grades, including azeotropic (*i.e.*, containing water), denatured (*i.e.*, containing an additive), and

absolute (*i.e.*, pure or 100%).[20] [Myerson 761:1-15.] Drs. Hollingsworth and Lee, however, used only absolute ethanol. [Hollingsworth 102:19-24; 132:19-133:10; Lee 318:1-18.]

[056] Dr. Hollingsworth admitted that patent literature reflects a use of the term "ethanol" that could be interpreted more broadly than just absolute ethanol.[21] [217:6-218:5 (PTX-101-13 at 4:7-10), 218:6-25 (PTX-100-1 at Abstract), 219:15-221:2 (PTX-124-13).] This general use is further reflected in organic chemistry laboratory texts. [212:6-214:4 (PTX-589-8); 214:9-215:7 (JTX-56-6 at Tbl. 3-2).] Accordingly, a narrow interpretation of ethanol as synonymous with absolute ethanol is by no means the sole, universally accepted definition.[22]

[057] Importantly, the '570 Patent and experiments performed by Cephalon show that different polymorphic forms of armodafinil can result from recrystallization from different grades of ethanol, for example that the use of denatured ethanol under at least some conditions can lead to Form II. [JTX-1-32 at 27:23-47; JTX-1-33 at 29:30-51; JTX-120-4 at ¶ 13; Mallamo 657:11-658:5.] Given that the grade of ethanol used for recrystallization can affect the final product, the failure by Defendants' experts to test other grades of ethanol renders their testing insufficient to establish Form I as the necessary and inevitable product of Preparation I.

c. Defendants' Experts Used Only One Cooling Rate

[058] Preparation I does not specify the method or rate of cooling of the armodafinil/ethanol solution during the "recrystalliz[ation] from ethanol" in step (d). The

[20] The '570 Patent also describes more than one type of ethanol, including absolute ethanol, ethanol/water mixture (azeotropic), and denatured ethanol. [JTX-1-32 at 27:24-43.]

[21] Other patents by Louis Lafon, inventor of the '855 Patent, also show that he distinguished the more broad term "ethanol" from "absolute ethanol." [*Compare* PTX-139-3 at 4:45-47; PTX-139-5 at 7:1-3, 53-55; PTX-139-6 at 9:46-48 *with* PTX-139-3 at 3:61-65; 4:13-14].

[22] The proper interpretation of term "ethanol," at best, depends upon the totality of the circumstances. [*See, e.g.,* Myerson 765:14-773:1 (explaining a different interpretation of "ethanol" in a case involving a polymorph patent specifically discussing solvent mixtures).] Thus, documents relied upon by Dr. Hollingsworth to limit ethanol to absolute ethanol are distinguishable because, unlike the context of those references, ethanol is not used in the '855 Patent for a therapeutic purpose or as an excipient. [210:13-212:5; JTX-116-5; JTX-28-3.]

method of cooling used, which controls the cooling rate, can affect the polymorphic form of the recrystallization product. [Hollingsworth 157:16-158:7, 226:20-227:10; JTX-27-13; Bernstein 565:8-566:19; Myerson 750:10-752:12.] Despite the fact that multiple cooling methods would have been reasonable, Defendants' experts used only one form of cooling in their experiments.

[059] Dr. Hollingsworth used only very slow cooling [Myerson 750:10-752:14 (PDX-5-16)], which resulted in an overall temperature change on the order of about 0.3°C per minute [Hollingsworth 179:1-181:3]. Dr. Lee was instructed by Defendants' counsel to use slow cooling [297:18-25, 309:7-12], resulting in an average cooling rate of 0.55°C per minute [324:24-327:4, 327:9-11, DTX-212-12 ll. 2-9].

[060] Notably, the '570 Patent, which Dr. Hollingsworth and Dr. Lee read prior to conducting their experiments [Hollingsworth 159:1-19; Lee 281:18-20], explains that a crystallization using ethanol and slow-cooling at a rate of 0.6°C per minute or less—just as Dr. Hollingsworth and Defendants' counsel selected—is preferred to crystallize Form I armodafinil [JTX-1-21 at 5:50-56, -22 at 7:1-6].

[061] Yet there were multiple, reasonable cooling methods available to skilled artisans. For example, standard references teach that the recrystallization solution may be simply "set aside to cool until crystals are formed" [JTX-56-8], or that more rapid cooling may be used [JTX-15-8]. Indeed, the testing that Cephalon presented to the PTO indicates the use of such bench top, room temperature cooling [JTX-120-19 (Example No. 5/2502)], as well as more rapid cooling in an ice bath [JTX-120-20 (all four examples)]. Dr. Hollingsworth admitted that those different methods may be appropriate under certain circumstances [176:2-177:2], and that the literature encourages the use of rapid cooling to obtain fine crystals [172:23-173:14, JTX-15-8]. In fact, Dr. Hollingsworth admitted that the use of rapid cooling "is a recipe for actually making other forms." [131:13-132:14.] Dr. Myerson confirmed that cooling in an ice bath—as

Cephalon did with armodafinil to achieve fine crystals—is not unusual. [742:8-24 (PTX-386-5).] Dr. Lee also admitted that bench top cooling was reasonable. [321:11-323:18.]

[062] Accordingly, Defendants' use of only slow cooling is not representative of the full scope of the '855 Patent and is insufficient to find inherency of Form I.

E. Products Generated at Intermediate Stages of Preparation I Are Irrelevant

[063] Dr. Hollingsworth contends that he obtained Form I armodafinil after methanol evaporation and ether wash in both Runs 1/2 and 3/4. [115:11-117:24.] Aside from having been rebutted by the testing of Drs. Smith and Selbo [*see* FOF 26], these incomplete results fail to establish that practice of Preparation I necessarily and inevitably produces Form I. For example, Dr. Hollingsworth admits that he did not heat the solution to 30-40°C for dissolution as called for in step (b). [*See* FOF 47.] Because these products are not the result of an accurate reproduction, and are in any event refuted by the experiments of Drs. Smith and Selbo, they cannot be said to be the inevitable product of Preparation I.

[064] In addition, for the Run 3/4 material after methanol evaporation, Dr. Hollingsworth admitted that the XRPD did not have the particular peaks for Form I claimed in the '570 Patent [247:10-248:16], and agreed that it would be "difficult" to say that this sample meets the recited requirements of Form I [248:17-21]. This product was subjected to extensive vacuum drying [Hollingsworth 247:10-248:9], that was neither taught in Preparation I nor done in Run 1/2. Moreover, Dr. Hollingsworth failed to establish the pharmaceutical acceptability of the impurities present in these intermediate samples. [FOF 30, 31.] These additional inconsistencies show that these intermediate products are not probative of inherent anticipation.

V. Conclusions of Law Showing a Lack of Inherent Anticipation

[065] An issued patent is presumed valid. 35 U.S.C. § 282; *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed. Cir. 2004); *Hybritech Inc. v. Monoclonal*

Antibodies, Inc., 802 F.2d 1367, 1375 (Fed. Cir. 1986). A party challenging the validity of a patent claim has the burden of overcoming the presumption of validity by "clear and convincing" evidence,[23] and that burden never changes. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2243 (2011). When the PTO examiner considered the asserted prior art during prosecution, the burden placed on the challenger is particularly difficult to satisfy. *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004).

[066] To anticipate a claim and render it invalid, a single prior art reference must expressly or inherently disclose each and every element as set forth in the claim. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). In other words, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1293 (Fed. Cir. 2009), *cert. denied*, 130 S. Ct. 1052 (2010).

[067] Inherent anticipation "requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec*, 295 F.3d at 1295 (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939)). To be inherent, an undisclosed feature must "necessarily and inevitably" flow from practice of what is disclosed. *Schering*

[23] The clear and convincing evidence standard also applies to an obviousness challenge. *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1336 (Fed. Cir. 2010).

Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1378 (Fed. Cir. 2003) (finding inherent anticipation of bare compound claims to a metabolite that the trial record showed was "a necessary consequence of administering [the prior art parent drug] to patients," and noting that pharmaceutical composition claims including the metabolite may still be patentable); *Pfizer, Inc. v. Teva Pharm. U.S.A., Inc.*, No. 09-cv-307 (GMS), 2012 WL 2951367, at *25-28 (D. Del. July 19, 2012) (finding no inherent anticipation where Defendant's reproductions did not use the reagent specified in the prior art process, and did not perform adequate analytical testing); *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) (finding no inherency based on what would result due to optimization of conditions, which was necessarily present in the prior art).

[068] In other words, if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art does not inherently anticipate. On point here, the Federal Circuit has upheld a finding of no inherent anticipation where testing evidence showed that a prior art example could yield crystals of either the claimed polymorph or a different polymorph. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995). As in that case, Defendants' experimentation here shows that a composition "consisting essentially of" Form I armodafinil is not the necessary and inevitable product of Preparation I. Dr. Hollingsworth's Run 3/4 experiments show either mixtures of Form I with other unknown crystalline material or, when using a higher concentration of solute, mostly Form II armodafinil. [FOF 29.] Under the Court's claim construction, claims 6 and 9 require a composition having only Form I armodafinil as the pharmaceutically active component. [FOF 20.] Dr. Hollingsworth acknowledged that his mixture of armodafinil forms does not "consist essentially of" Form I. [FOF 29.] Defendants' testing shows that a reasonable "recrystallization from ethanol" does not produce a product within the scope of the asserted claims, discounting any evidence that Preparation I would necessarily and inevitably anticipate those claims.

[069] Drs. Hollingsworth, Lee, and Robie further admitted that they did not identify or quantify impurities in their samples. [FOF 30, 31, 32.] The presence of these unknown impurities disqualifies their samples as "pharmaceutical compositions" fit for human use, as they have not proven that these impurities are "pharmaceutically acceptable ingredients" as required by the Court's construction of claims 6 and 9. [FOF 20.]

[070] Defendants' experts also did not accurately reproduce Preparation I. Neither Dr. Hollingsworth nor Dr. Lee used the dissolution temperature of 30-40˚C in step (b), as expressly directed. [FOF 47.] Thus, their testing cannot support any conclusion that Form I armodafinil is the inevitable or natural result of Preparation I. *See Valeant Int'l (Barbados) SRL v. Watson Pharm., Inc.*, No. 10-20526-CIV, 2011 WL 6792653, at *5 (S.D. Fla. Nov. 8, 2011) ("Thus, because Dr. Adlington did not follow the explicit disclosure of Example 1 of the Mehta patent, his experiment is simply not probative of the issue of inherent anticipation, as it clearly does not demonstrative that Form I bupropion hydrobromide is the 'natural result flowing from the explicit disclosure of the prior art.'"); *Glaxo Group*, 376 F.3d at 1348-49.

[071] The testing by Drs. Hollingsworth and Lee also is not representative of the full scope of reasonable experimental possibilities in Preparation I and is insufficient to prove anticipation. *Sensormatic Elecs. Corp. v. Tag Co. US, LLC*, 632 F. Supp. 2d 1147, 1159-61 (S.D. Fla. 2008) (where varying the "broad ranges of processing techniques" in the prior art patent steps could affect the properties of the final product and result in a "broad universe of materials," finding no inherent anticipation because "the fact that some embodiments of the '399 patent may contain all the limitations of an asserted claimed does not preclude the possibility that some limitations may be absent in other '399 embodiments"). Because the '855 Patent does not disclose many details for its procedure, skilled artisans would have to use their judgment to complete the experiment. [FOF 50.] Differences, even slight ones, in procedure may lead to

differences in the form of armodafinil produced. [FOF 49, 50.] Defendants' experts, however, used only limited set of testing parameters in their experiments [FOF 53, 55, 58], which after reading the '570 Patent they would have understood to favor the formation of Form I [FOF 53, 60]. *See Glaxo Group*, 376 F.3d at 1348-49 (finding lack of inherent anticipation where expert had read the patents-in-suit prior to conducting experiments and benefitted from that hindsight knowledge when practicing missing claim limitations in the prior art).

[072] In particular, as to the "recrystallization from ethanol" in step (d) of Preparation I, Dr. Hollingsworth used only absolute ethanol [FOF 55], low armodafinil concentrations [FOF 53], and very slow cooling [FOF 59]. Dr. Lee also used only absolute ethanol [FOF 55], and, as instructed by Defendants' counsel, slow cooling [FOF 59] and the same low concentration that Dr. Hollingsworth used [FOF 53]. Notably, Drs. Hollingsworth and Lee had both read the '570 Patent, which teaches these very procedures, prior to conducting their experiments. [FOF 53, 60] *See Glaxo Group Ltd. v. Apotex Inc.*, 268 F. Supp. 2d 1013, 1032 (N.D. Ill. 2003) ("The court finds it highly significant that Dr. Siegel had been given and read the '181 patent prior to performing his experiments. Dr. Siegel knew what result he needed to reach. Thus, even if he was acting in the best of faith, that knowledge likely had an effect on his decision, making the credibility of his experiments highly suspect."); *aff'd*, 376 F.3d at 1349 ("It was therefore not incorrect for the district court to discredit Dr. Siegel's testimony and experiments as to whether the '320 patent inherently yields highly pure amorphous CA."). Skilled artisans also would not restrict Preparation I to only absolute ethanol. [FOF 55, 56, 57.] In addition, skilled artisans would use various cooling methods and rates and solute concentrations, and different types of ethanol, different solute concentrations, and different types of cooling during a "recrystallization from ethanol" may lead to different armodafinil polymorphs, as demonstrated by the evidence at trial and the PTO declarations. [FOF 50, 54, 57, 61.] Accordingly, Defendants' limited testing

does not show that Form I armodafinil is the necessary and inevitable result of Preparation I, given the various ways one of ordinary skill in the art may interpret its disclosure.

[073] Defendants' experts did not perform the instantaneous melting point test needed to show their products were the same as those made by Preparation I. [FOF 39.] Other melting point testing shows widely variant results that could not be correlated to instantaneous melting point. [FOF 40.] Because Defendants' experts did not use the correct test, there is no clear and convincing evidence that their products are the same as that obtained in Preparation I, rendering those tests incapable of showing whether Form I is a necessary and inevitable result.

[074] The reproductions of Preparation I performed by Defendants' experts had yields that were far lower than reported in the '855 Patent, indicating the preparation of products with different impurity profiles. [FOF 42, 43, 45.] Evidence presented at trial shows that the presence of impurities can affect the polymorphic form of the product obtained. [FOF 45, 50.] The difference in yield shows that Defendants' products have different impurity profiles, further indicating that their reproductions were not representative of Preparation I.

[075] The '855 Patent was before the PTO during prosecution of the '570 Patent. [FOF 13.] In allowing the patent, the PTO found persuasive Cephalon's testing showing that different methods for practicing "recrystallization from ethanol" may result in different polymorphic forms. [FOF 13.] While the PTO did not have Defendants' testing to consider, that testing only involved a limited set conditions that do not refute the testing provided by Cephalon. [FOF 48.] Moreover, Cephalon presented evidence to the PTO showing that Form I armodafinil does not have an instantaneous melting point consistent with the melting point of Preparation I [FOF 37], and Defendants did not provide any rebuttal testing [FOF 39, 40]. The evidence presented to the PTO and the PTO's decision to allow asserted claims 6 and 9 further show that Defendants have not proven inherent anticipation by clear and convincing evidence.

CLAIMS 6 AND 9 ARE NOT OBVIOUS OVER THE '855 PATENT

[076] At trial, Defendants contended that claims 6 and 9 would have been obvious in view of a single piece of prior art, the '855 Patent,[24] and presented a single expert witness, Dr. Michael Cima.[25] Defendants specifically argue that: (1) there was motivation and reasonable expectation to conduct crystallization experiments to make the "most stable form" of armodafinil, which in hindsight is currently Form I, and (2) the use of Form I in a pharmaceutical composition would have been obvious. [Cima 381:2-24, 382:19-383:1, 433:20-434:9.] Defendants do not rely on any teaching or suggestion of specific experimental conditions to yield a material consisting essentially of Form I.

[077] Dr. Joel Bernstein responded on behalf of Plaintiffs, and fully rebutted Dr. Cima's opinions.[26] Dr. Bernstein is an expert on the polymorphism of molecular crystals. [482:11-494:8; *see* Hollingsworth 206:13-22.] Now a Professor of Chemistry at New York University in Abu Dhabi, he has spent over 40 years studying polymorphism. [482:11-13, 485:2-486:5.] He is the author of "Polymorphism in Molecular Crystals" [PTX-585], which was published contemporaneously with the '570 Patent and reflects the state of the art at that time [491:7-492:6]. That book has been cited nearly 1,000 times, including by Dr. Cima [551:7-11] as well as the '570 Patent itself [491:20-492:6; JTX-1-21 at 6:54-58]. Among his other 180 publications on polymorphism, Dr. Bernstein authored a 2011 article [PTX-28] that updates the state of the art in the decade since his book. [492:15-493:20, 490:14-491:3; PTX-16-6-23.]

[24] Defendants did not rely upon secondary references to be combined with or modify the '855 Patent. [*E.g.*, Tr. 28:14-18; Cima 381:2-383:24, 425:1-16.]

[25] *See* Tr. 369:24-370:8 ("Up until this point, you have been hearing live witnesses on inherent anticipation. Dr. Cima is going to talk about obviousness."); *see also* Tr. 61:2-8.

[26] Dr. Cima's opinions on obviousness at trial were in part refuted by his own prior publications and the literature as a whole. For example, his extreme and unsupported opinion that only metastable forms are unpredictable, but that these are not used in pharmaceuticals [442:20-21], is disproved by respected authorities, on which Dr. Cima actually relied, and the experience in the field. [398:14-21; Bernstein 525:11-526:3, 526:20-527:20; JTX-27-4.]

[078] As Dr. Bernstein explained, the field of polymorphism is highly unpredictable, with each molecule presenting what is essentially a new situation. [548:1-549:16; PTX-585-0126.] A general motivation to experiment with conditions that might or might not yield unknown crystal forms is not a teaching or suggestion of Form I, much less a pharmaceutical composition consisting essentially of Form I as the active pharmaceutical ingredient. Defendants' arguments based on a general motivation to experiment is also deficient because the prior art did not teach any limited set of conditions with which to experiment. Accordingly, Defendants have not met their burden to prove that claims 6 and 9 are obvious.

VI. Findings of Fact Related to Non-Obviousness

A. Form I Was Not Reasonably Predictable

[079] The prior art disclosure of armodafinil, which consisted of the '855 Patent, did not provide any basis for a skilled artisan[27] to have predicted whether armodafinil would crystallize in polymorphic forms or what the structure of any of those forms might be, much less a basis to have predicted Form I.[28] [Bernstein 496:3-503:2, 511:17-25, 547:16-18, 548:1-551:14, 562:16-563:17, 586:9-588:22.] Due to the fundamental unpredictability of polymorphism and the uniqueness of armodafinil, a skilled artisan around 2002 would not have had a reasonable expectation that armodafinil is polymorphic. [Bernstein 547:22-25, 548:1-20; PTX-585-126.]

[080] The overriding unpredictability is reflected in Dr. Cima's own publications,

[27] A person of ordinary skill in the art would have a bachelor's degree in chemistry, chemical engineering, or related disciplines and either (i) at least three years experience related to organic synthesis, API manufacturing and formulation, or detection and/or evaluation of solid state forms in the pharmaceutical industry or (ii) an advanced degree in chemistry, chemical engineering, or related disciplines. The conclusion that Form I would not have been obvious does not turn, however, on the specific contours of this definition; Form I would not have been reasonably predictable regardless of the level of expertise. [Bernstein 545:11-547:15.]

[28] Background references cited by Dr. Cima show no more than, at most, the state of the art related to crystallization techniques and a general motivation to discover new crystal forms of a pharmaceutical compound through trial and error experimentation. [392:19-393:23; 395:21-397:15; 397:22-399:5; 402:12-404:10; 407:17-412:6.]

which contradict Defendants' contentions in this case and further evidence that there was no narrow set of conditions for polymorph crystallization experimentations:

- "There are no failsafe methods to predict the extent of polymorphism of a given compound." [JTX-35-1];
- "Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of… polymorphs have defied prediction." [JTX-7-22; *see also* JTX-7-3 (listing in Table 1 over 30 of the most notable composition and processing variables that can affect polymorphic form)]; and
- "Experiments are performed at small scale to reduce the material demand and to afford the largest number of conditions possible. The large number of crystallization trials performed in these experiments reflects the reality that nucleation rate has an extremely non-linear dependence on the experimental conditions, and as such, the probability of a ***chance occurrence*** of a particular form is increased by a [high throughput] approach." [JTX-7-4 (emphasis added)].

[081] Other publications and the experience of persons actually working in the field at the relevant time further confirm that crystallization and polymorphism were not predictable. [Bernstein 551:12-14; Blomsma 823:23-824:12; Coquerel 836:23-837:4, 843:9-18.] For example, a 2001 paper by Dr. Zaworotko[29] characterized efforts to predict crystal structures as "continu[ing] to represent a challenge of the highest level of scientific and technological importance," given that "it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition[.]" [JTX-86-2.]

[082] The unpredictability of polymorphism extends beyond being unable to predict whether and what crystals might be possible to make. [Bernstein 496:3-500:18.] The crystal structure itself is fundamentally unpredictable. As Dr. Cima conceded, neither the specific structure of Form I, *i.e.,* the physical dimensions within the crystal and corresponding interplanar XRPD limitations of claim 6, nor its properties would have been reasonably predicted. [420:12-

[29] Dr. Zaworotko had been retained as an expert by Defendants in this case, and submitted expert reports on their behalf. [*See* PO Ex. I.]

421:17, 435:15-436:25; Bernstein 505:8-10, 505:20-507:7 (PDX-1-13), 587:21-588:22 (PDX-1-18).] Even if there was some way of predicting that a compound would be polymorphic and what the crystal structures might be, a person of ordinary skill would still not know how to make a specific polymorph or predict its properties. [Bernstein 500:11-18, 548:1-549:5.]

[083] Because the existence, structure, and methods of making polymorphs were not predictable, crystal forms could only be prepared and identified by trial and error experimentation. [Bernstein 555:9-556:3, 571:24-572:12; Cima 447:8-12; Hollingsworth 233:3-234:3 (JTX-18-43).] Dr. Cima repeatedly expressed the same understanding in his peer-reviewed publications. [PTX-26-4 ("[T]he only manner in which one can be assured of having a complete knowledge of the polymorphic landscape on which to base a development choice (usually the most thermodynamically form) is to subject the API to a variety of crystallizing conditions that can expose the diversity of forms."); JTX-7-22 ("[D]iscrete crystal forms are considered non-obvious and patentable" and, due to their unpredictability, "in order to obtain patent protection on these forms… it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials.");[30] Cima 468:4-8.]

[084] For armodafinil in particular, even highly experienced researchers working in the field could not have predicted whether it would exhibit polymorphism or what recrystallization conditions would generate a particular crystalline form or solvate. [Coquerel 828:18-21, 829:2-9, 829:13-830:10, 841:25-843:2; Myerson 732:24-733:12, 734:17-25, 757:22-759:11; Bernstein 547:4-15.]

[085] In sum, a skilled artisan could not have reasonably predicted anything about the

[30] Dr. Cima admitted that the statements of unpredictability and patentability in his 2004 article are not limited to metastable forms. [467:6-468:3; JTX-7-22.] In any event, one cannot know if Form I is the actually the most stable polymorph of armodafinil. [Hollingsworth 229:6-230:2; Bernstein 510:2-511:16 (PDX-1-16, PDX-1-17).]

polymorphism of armodafinil, much less Form I or a pharmaceutical composition consisting essentially of Form I, prior to conducting unpredictable trial and error experimentation. [Bernstein 549:6-9.]

1. The '855 Patent Did Not Make Form I Reasonably Predictable

[086] The unpredictability of polymorphism is particularly acute for armodafinil given the limited prior art. This enantiomeric molecule is mentioned in only one prior art reference, the '855 Patent, which does not have any teaching or suggestion of Form I. [Bernstein 630:8-12; Mallamo 653:21-654:4; Coquerel 837:25-838:2; Blomsma 822:25-823:6.] Nor does the '855 Patent teach or suggest that armodafinil is polymorphic. [Bernstein 547:16-21.] In fact, prior to the '570 patent-in-suit, there was no disclosure of Form I armodafinil or anything to indicate that Form I armodafinil was the most stable form. [Bernstein 571:7-12.]

[087] Beyond the absence of any express disclosure, there is also no implicit disclosure of Form I reported in the '855 Patent.[31] First, while the result of Preparation I is described as being "in the form of white crystals" that was "recrystallized from ethanol" [JTX-103-3 at 3:51-54], the '855 Patent is silent as to whether it may or may not have been a solvate, hydrate, a mixture of materials, or a different form of armodafinil. [Bernstein 553:7-21; Coquerel 838:3-839:7.] Further, other than stating "recrystallized from ethanol," the '855 Patent does not specifically address any of the multitude of crystallization conditions in Table 1 of Dr. Cima's paper, JTX-7. [Bernstein 567:6-9.] Nor does the '855 Patent give any indication of what thermal conditions might lead to what we now call Form I. [Bernstein 566:25-567:5.]

[088] Second, the reported melting point for the Preparation I material [JTX-103-3 at

[31] Neither would the polymorphism of armodafinil generally nor Form I in particular have been reasonably predictable from the potential pharmaceutical use disclosed in the '855 Patent. [Bernstein 569:16-20.] To the contrary, pharmaceutical compounds are no more polymorphic than other compounds, a fact addressed in the peer-reviewed literature by Dr. Bernstein and others. [Bernstein 493:21-494:1, 569:21-571:1; PTX-28-2.]

3:55] does not indicate whether or not armodafinil could be polymorphic and is consistent with the material being a solvate. [Bernstein 554:3-10.] The existence of solvates is not a hypothetical, as it was later discovered that an ethanol solvate of armodafinil may be formed. [Hollingsworth 252:17-253:14; PTX-129-3.] Thus, the '855 Patent disclosure of "white crystals" prepared from ethanol would not have suggested to a skilled artisan that armodafinil is polymorphic; "white crystals" does not disclose any information beyond the material being "white crystals." [Bernstein 562:16-563:7; Coquerel 838:23-839:7.]

2. Molecular Structure Did Not Make Form I Reasonably Predictable

[089] The molecular structure of the armodafinil molecule was known based on the '855 Patent, but provides no basis to predict polymorphism of armodafinil or Form I. [Bernstein 556:4-14.] The inability to predict polymorphs from molecular structure is reflected in the literature and not contradicted by any material relied upon by Dr. Cima.

[090] For example, an article by Professor Gautam Desiraju—one of the leading researchers in organic solid-state chemistry—explained that there were "major obstacles in routinely predicting crystal structure from molecular structure," including that "the crystal structures of many 'simple' organic compounds need not be simple at all" and "chemists seem unable to accurately foresee" how functional groups on a molecule will interact to form crystals. [JTX-23-2; Bernstein 556:15-558:9; *see also* JTX-86-2.]

[091] The inability to predict polymorphism from a molecule's functional groups is also reflected in Dr. Bernstein's 2011 article, which explained that there is no evidence of a correlation between the number of hydrogen-bonding functionalities and the tendency to form multiple crystal forms.[32] [PTX-28-12; Bernstein 560:24-562:15.]

[092] Concrete examples provided by Dr. Bernstein further evidence the inability to

[32] Dr. Cima's assertions to the contrary were unsupported. [439:7-25; Bernstein 559:25-562:15.]

predict polymorphs from molecular structure. As he explained, neither sucrose nor ibuprofen were known to be polymorphic, despite having been prepared in large quantities for long periods of time. [558:14-559:19 (PDX-1-14).] Dr. Bernstein thus explained that there was no way to predict whether armodafinil would be consistent or inconsistent with the absence of known polymorphism for sucrose and ibuprofen. [Bernstein 559:20-560:23 (PDX-1-14).]

3. Modafinil Did Not Make Form I Armodafinil Reasonably Predictable

[093] Contrary to Dr. Cima's assertions, neither the polymorphism of armodafinil nor Form I was reasonably predicable based on polymorphism of racemic modafinil. Firstly, there is no evidence in the prior art that racemic modafinil is polymorphic.[33] Secondly, there is no evidence that a polymorphic racemate would suggest a polymorphic enantiomer. [Bernstein 547:22-25; 548:1-20.] Indeed, Dr. Cima did not cite any studies indicating that polymorphism of a racemic mixture is predictive of polymorphism in a single enantiomer. [Bernstein 567:19-23.] Dr. Bernstein, who has studied and written extensively on polymorphism, was not aware of any support for Dr. Cima's theory; Dr. Bernstein instead provided concrete examples of cases where the racemic compound exhibits polymorphism but the enantiomer does not. [Bernstein 567:24-569:9 (PDX-1-15); JTX-8-10 (racemic crystals preferred over enantiomeric crystals).]

B. Form I Could Not Have Been Predicted Based on Any Alleged Motivation to Obtain a "Most Stable" Form of Armodafinil

[094] Defendants base their contention that claims 6 and 9 would have been obvious on the premise that Form I is the "most stable" crystalline form of armodafinil and by arguing that the "most stable" form of any compound would have been predictable and easily obtained.[34]

[33] Defendants withdrew the one piece of evidence in support of their argument, JTX-11, as they could not establish it to be prior art. [*See* 413:19-415:24.]

[34] The designation of a crystal as the "stable form" or "most stable form" does not mean that other forms, so-called "metastable" forms, are unstable. Metastable (higher-energy) forms of a

[Cima 381:13-382:18; Bernstein 571:2-6.] However, Defendants' allegations of motivation for and predictability in obtaining a hypothetical "most stable" form of armodafinil are not equivalent to a motivation for or prediction of the specific crystal now designated as Form I armodafinil, its structure, its method of making, or its aggregate of properties.

[095] First, the "most stable" form of a crystal does not refer to a specific material. It is a relative term and refers conceptually to the lowest energy crystalline form known at any given time. [Bernstein 510:2-511:16 (PDX-1-16, PDX-1-17).] As new crystals are developed, the designation of which form is "most stable" can and does change, and it is impossible to know if the absolutely "most stable" form of a crystal has been developed. [Bernstein 510:2-511:25 (PDX-1-16); PTX-26-4 (trial-and-error testing was the "only manner in which one can be assured of having a complete knowledge of the polymorphic landscape…").] In fact, Form I is not necessarily the absolutely most stable form of armodafinil, but is only the most stable of the ones that have been found to date. [Bernstein 507:14-23, 512:10-513:16.] Indeed, the later discovery of a more stable form was exactly what occurred for the AIDS drug ritonavir, where a more stable form, Form II, was unintentionally and unpredictably produced after extended commercial use of the less stable but more useful Form I. [Bernstein 531:9-533:4; Myerson 733:16-734:16; Cima 396:12-397:21; JTX-104-1.]

[096] Second, Dr. Cima's description of alleged motivation is nothing more than a generalized research goal of developing new and improved crystalline forms and does not render obvious any specific solution, much less Form I. It is no different than a motivation to find an effective drug with the lowest toxicology profile, which likewise does not render obvious a specific drug that has the lowest toxicology profile. [Bernstein 572:24-573:12.]

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material do not always convert to more stable (lower-energy) form, with diamond, a metastable form of carbon, being just one example. [Bernstein 507:24-510:1 (PDX-1-16).]

[097] Third, Dr. Cima's contentions of predictability are unsupportable. [Bernstein 571:2-19.] It is no more than a logical truism that there will always be a "most stable form" if a molecule can be made to crystallize, just as there will always be a tallest child if a couple has children. However, while one could therefore "predict" that if a couple had children one would be the tallest, this does not in any way identify which future child will be the tallest. [Bernstein 512:7-13.] It is not a prediction of the child per se. Likewise, the "prediction" that crystallization experiments might yield the most stable form—again a relative term based on the crystal forms known at any given time—does not identify or predict a specific crystal form. [Bernstein 511:14-25; 512:25-513:3.]

[098] Fourth, Defendants' argument is based on improper hindsight. Prior to the '570 Patent, there was no disclosure of Form I armodafinil at all, or anything to indicate that Form I was the most stable form. [Bernstein 571:7-12.] Thus, the only link between a "most stable" form and Form I is the '570 Patent-in-suit.[35] In fact, Form I would not be predictable based on its relative stability, as these relative energies are not predictable. [Bernstein 511:17-25.]

[099] Fifth, Defendants' suggestion that a skilled artisan would focus on the "most stable" form of armodafinil and that this made Form I reasonably predictable is contrary to the practice in the field. Other considerations, beyond thermodynamic stability, go into the selection of a polymorph or solid form for use in a pharmaceutical product. [Bernstein 513:17-20, 617:11-23; Cima 441:22-442:16; Hollingsworth 224:9-226:19.] Consequently, some drug products employ metastable or amorphous forms of the API because the "most stable" form has undesirable characteristics. [Bernstein 530:8-11.] For example, a solid material must be

[35] Defendants may attempt to rely upon the experiments conducted by Cephalon to demonstrate that crystallization of armodafinil will often result in Form I. As these experiments are not prior art, such reliance would also be improper hindsight, as this Court ruled when it precluded testimony on the subject from Dr. Cima. [Tr. 419:9-420:10.]

sufficiently soluble for its intended pharmaceutical use. [Coquerel 832:22-833:4; Bernstein 522:5-525:7; Mallamo 676:10-18.] Yet, solubility and stability are inversely related: the more stable the polymorph, the less soluble it will be. [Bernstein 529:3-530:7.] Ritonavir is an example where the later-discovered "most stable" form was very undesirable due to its low solubility. [Bernstein 531:9-532:7.] Similarly, the more stable polymorph of chloramphenicol palmitate has almost no bioavailability, making it effectively useless compared with the less stable form. [Bernstein 522:5-525:7.]

[0100] Finally, even if a "most stable" crystal form could have been predicted, a skilled artisan would have expected to have to resort to trial and error experimentation, using a large number of conditions, to try to make this form. [Bernstein 500:11-18.] Thus, no defined, finite set of reasonably predictable experiments would have been available to seek to make this form.

C. Form I Could Not Have Been Reasonably Predicted Despite an Alleged Motivation to Perform Crystallization Experiments

[0101] Defendants' contention that there would have been a motivation to study armodafinil for polymorphs does not render obvious any specific form, much less a pharmaceutical composition consisting essentially of Form I as specified in claims 6 and 9 of the '570 Patent-in-suit. It is no different than a motivation to screen the toxicology of a pharmaceutical compound, which is standard practice but does not make the actual results of the screen in any way predictable. [Bernstein 572:24-573:17.] Indeed, rather than making polymorphs predictable, trial and error crystallization experimentation is used ***because*** polymorphs are ***un***predictable. [Bernstein 571:24-572:23; Blomsma 823:7-14.]

1. Polymorph Crystallization Experiments Required a Vast Number of Testing Parameters

[0102] Crystallizing new polymorphs often requires hundreds to thousands of experiments that analyze the effects of various critical parameters such as temperature, solvent

and solvent mixtures, mixing time, cooling rates, stirring rates, and concentrations, as well as methods and processes for precipitation, cooling, evaporation, slurry, and thermo-cycling. [JTX-18-43 at ¶ 6; Bernstein 575:18-576:21.] For example, a May 2002 article co-authored by Dr. Cima shows that, at that time, 7776 crystallization experiments, representing 2592 unique conditions, were used in experiments for polymorphs of acetaminophen. [JTX-35-2; Bernstein 580:23-581:9; 582:3-19, 583:8-13; PTX-38-3.] And for each solvent system, several other parameters would be varied, including the heating parameters, cooling, stirring, etc. [Bernstein 583:14-18.] The large number of conditions used reflects the fact that even Dr. Cima and the other authors of JTX-35 could not predict which conditions to use or the results of their experiments. [Bernstein 582:20-25.] The unpredictability of polymorph crystallization further required the use of multiple replicates. [JTX-35-2.] Specifically, these experiments were run in triplicate because crystallization results are not necessarily reproducible even under seemingly identical conditions. [Bernstein 583:19-585:19; Blomsma 823:15-22.]

[0103] The number of crystallization conditions was so large that they could not be practically achieved by persons of ordinary skill prior to the filing date of the application leading to the ’570 Patent. This fundamental limitation is reflected in the 2002 patent application from Dr. Cima, which states that “[a]t present, industry does not have the time or resources to test hundreds of thousands of combinations to achieve an optimized solid form[]. At the current state of the art, it is more cost effective to use non-optimized or semi-optimized solid-forms in pharmaceutical and other formulations.” [PTX-27-12 at ¶ 30; Bernstein 579:17-580:16.] Dr. Cima’s litigation testimony that only metastable forms, which he contends are not used in pharmaceuticals, are unpredictable is not credible. [*See* Cima 442:20-21, 465:7-468:3.]

2. The Prior Art Contains No Specific Teaching Directed to Crystallization Experiments for Armodafinil

[0104] There was no specific teaching or suggestion in the prior art to study armodafinil polymorphism, notwithstanding the 12 years between publication of the '855 Patent on the enantiomer and the filing of the application for the '570 Patent. [Bernstein 573:21-574:4.] Nor did the art teach or suggest a limited number of test conditions (*e.g.*, solvents; concentrations; cooling, heating, and stirring rates) that would be tested in screening experiments for armodafinil.[36] [Bernstein 574:5-23, 575:11-17; Coquerel 831:21-832:11.] And there was no way to predict the outcome of any of the vast number of possible conditions that could have been chosen. [Bernstein 573:13-20; 575:11-14; 586:9-20.] The selection of a certain set of conditions, but not others, could have resulted exclusively in forms other than Form I or mixtures of forms. [*See*, *e.g.*, JTX-38-42 (describing conditions for Example No. ON II/149 H, which yielded Form II); Hollingsworth 198:1-10; 210:5-12; Robie 366:19-25.]

3. Aging Experiments Were Not a Generally Applicable Method to Obtain a Material's Most Stable Crystal Form

[0105] Defendants point to the various "aging," "slurry," or "solvent-mediated transformation" methods of the Gu article as one experiment that could have been tried to obtain the most stable crystalline form of a compound. [JTX-104-1-2.] However, the article does not disclose any generally applicable method to obtain the most stable form. [Bernstein 630:18-24.]

[0106] At best, these slurry experiments can convert a mixture of forms to the most stable form ***already present in the mixture***, but not necessarily to the absolutely "most stable" form. [Bernstein 576:22-577:24.] Indeed, the Gu experiments were all based on pre-seeding the

[36] While the '855 Patent states that the product of Preparation I was "recrystallized from ethanol," it omits key information necessary to conduct a specific crystallization experiment. [*See* FOF 48, 49.] Further, the results of being "recrystallized from ethanol" were entirely unpredictable. [Bernstein 566:13-567:9; Hollingsworth 102:25-105:21.]

samples with 10% of the more stable Form II to induce transformation of the less stable Form I. [JTX-104-3 ("To determine the crystal growth rate of Form II, 90% of Form I and 10% of Form II were geometrically mixed…."); JTX-104-5, Table 1 ("Time (h)° for 10% Form II to Convert to 75% Form II").] However, Defendants have no evidence that Form I armodafinil would have been available in advance for use in such an "aging" experiment.

[0107] Moreover, notwithstanding the pre-seeding with the more stable form, Gu shows, and Dr. Cima admitted, that in nearly half of Gu's experiments there was no conversion of a less stable Form I to a more stable Form II. [JTX-104-5, Table I (see >360 hour induction times for the solvents ethanol, 2-propanol, water, acetic acid, dichloromethane, chloroform, water + acetonitrile 80%, and water + methanol 50%); Cima 456:18-457:9.] That is, even with pre-seeding, conversion did not occur in nearly half of the solvent systems, further evidencing that Gu's method is not a generally applicable method to obtain the most stable form of a material. [Bernstein 630:18-24; DTX-201-2 ("It is still unpredictable whether one polymorph will nucleate or grow faster than another from the same liquid, even with the knowledge of their structures and thermodynamic relations."); Hollingsworth 223:5-224:8.]

[0108] Thus, even if 10% of armodafinil Form I had been available for use in an experiment according to Gu, there would have been no reasonable expectation of success to convert a mixture of crystalline forms to a pharmaceutical composition consisting essentially of Form I as the active ingredient, as required by claims 6 and 9.

D. A Pharmaceutical Composition Consisting Essentially of Form I Would Not Have Been Obvious Based on Routine Purification Techniques

[0109] As admitted by Dr. Cima, the '855 Patent does not disclose the solid-state form of armodafinil used in its tablets and gel capsules or indicate that it consisted essentially of Form I. [460:5-9.] Dr. Cima's contention that routine techniques could be used to purify the product

of Preparation I is unsupported, and in any event would not be sufficient to show that purification would have yielded a pharmaceutical composition consisting essentially of Form I.

[0110] Many steps are required between making the product of Preparation I and making a tablet of armodafinil. [Cima 460:2-461:3.] Yet Dr. Cima provided no testimony and cited no evidence as to how these many steps could affect the material's crystal form. This is a critical omission since even seemingly small changes in processing conditions can affect a material's crystal form. [Bernstein 535:17-537:2; 564:19-565:7; 566:13-19; JTX-7-3 (table summarizing many, but not all, of the variables that can play a role in the crystallization process and affect the resulting polymorph); *see also* Mallamo 696:23-697:20.] This was proven by Dr. Hollingsworth, who converted a mixture containing mostly Form I to mostly Form II armodafinil by using a second recrystallization step, the key technique proposed by Dr. Cima to "purify" the product of Preparation I for pharmaceutical use. [Hollingsworth 195:16-200:22, 208:4-7 (CDX-1), 210:5-12; Cima 430:16-24; Myerson 749:11-19 (PDX5-14).]

[0111] For these reasons, Dr. Cima's contentions that the Preparation I product could be purified to yield a pharmaceutical composition consisting essentially of Form I fall short of proving obviousness. [Bernstein 541:5-542:8, 553:7-21; Coquerel 838:3-22.]

VII. Conclusions of Law Showing Non-Obviousness Over the '855 Patent

A. Form I Armodafinil Would Not Have Been Obvious Based on a General Motivation to Make New Crystal Forms

[0112] In this case, Form I would not have been obvious because there was no more than a general motivation to find new crystal forms of armodafinil with nothing directed to the unknown Form I itself. Indeed, for a patent challenger to establish obviousness, it is insufficient to allege a general motivation to discover an undefined solution that could take many possible forms. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 (Fed. Cir. 2008)

("[K]nowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method.").

[0113] "[T]he prior art did not and could not have suggested the particular structure" of Form I as there is no suggestion of the structure or method of making Form I armodafinil in the alleged prior art. *In re Certain Crystalline Cefadroxil Monohydrate*, 15 U.S.P.Q.2d 1263, 1269 (USITC 1990); *see also Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 1989 WL 147230, at *4 (Fed. Cir. 1989) (unpublished) ("[A] new crystalline form of a compound would not have been obvious absent evidence that 'the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form.'") (citing *In re Cofer*, 354 F.2d 664, 668 (C.C.P.A. 1966)). Specifically, Dr. Bernstein explained and Dr. Cima conceded that one could not have predicted the particular structure of Form I armodafinil. [FOF 82.] Likewise, nothing taught or suggested means of obtaining Form I, which is also unpredictable. [FOF 86.] Therefore, Defendants have not met their burden to show that claims 6 and 9 would have been obvious based on the alleged obviousness of Form I.

[0114] In *Pfizer, Inc. v. Apotex, Inc.*, the non-obviousness of crystal forms was held distinct from the obviousness of a pharmaceutically acceptable salt. 480 F.3d 1348 (Fed. Cir. 2007).[37] Unlike a general notion to find a new or improved crystal form, in *Pfizer* "it [was] not the case where the prior art teaches merely to pursue a general approach that seemed to be a promising field of experimentation or gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* at 1366 (quotations omitted). Instead, a limited number of pharmaceutically acceptable salt anions would have been known to the skilled artisan, who "was capable of further narrowing that list of 53 anions to a much smaller group . . . with a

[37] Dr. Cima's 2004 paper also recognizes the distinction between the unpredictability of polymorphs and the predictability of some salt forms. [FOF 80 (discussing JTX-7-22).]

reasonable expectation of success." *Id.* at 1367. The court's limited holding, based "on the *particularized facts of this case*," was that the "type of experiments used by Pfizer's scientists to *verify* the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to *discover* a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success." *Id.*

[0115] The non-obviousness of novel crystal forms is also distinct from the nucleic acid sequence at issue in *In re Kubin*, which the Federal Circuit found was directly related to, and determinable from, a naturally occurring polypeptide. 561 F.3d 1351, 1360-61 (Fed. Cir. 2009) (prior art "teach[es] a protein identical to NAIL, a commercially available monoclonal antibody specific for NAIL, and explicit instructions for obtaining the [claimed] DNA sequence for NAIL"). Indeed, unlike the prior art in *Kubin*, which taught "a five-step protocol for cloning [the claimed] nucleic acid molecules encoding" the known NAIL protein (561 F.3d at 1360), the prior art here had "no narrow set of conditions" and "no recipe for planning or designing a polymorph screen," the results of which are entirely unpredictable [Bernstein 574:20-575:17; FOF 104.] Importantly, the skilled artisan lacked any defined set of rules to determine how molecules can form into crystals. [Bernstein 498:17-500:10 (PDX-1-6 & 1-7).]

B. Defendants' Flawed "Obvious to Try" Argument

[0116] Defendants' contention based on allegedly "obvious to try" experiments to prepare the most stable form of armodafinil falls short of proving that Form I would have been obvious. "Obvious to try" is not equivalent to obviousness in every case, and is not in this case where the prior art provided at most general motivation to conduct trial and error experimentation in a decidedly unpredictable field. *Kubin*, 561 F.3d at 1359-60 (cautioning that "obvious to try" does not necessarily mean obviousness under § 103); *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011), *cert. denied*, 132 S. Ct. 1796 (2012) (rejecting

obvious to try argument because claimed invention would not have been an expected result).

[0117] "The Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008). Instead, "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [] 'identified, predictable solutions' may present a difficult hurdle [for patent challengers] because potential solutions are less likely to be genuinely predictable." *Eisai Co., Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008) (stating that the application of hindsight is inappropriate where the prior art does not suggest that the claimed subject matter could reasonably be expected to manifest the properties and advantages that were found).

[0118] That an invention would have been obvious as the "result of routine pharmaceutical development, not invention"—similar to Defendants' contentions here—has been rejected where the experiments were unpredictable. *Merck & Co., Inc. v. Sandoz Inc.*, No. 10-1625, 2012 WL 266412, at *2 (D.N.J. Jan. 30, 2012) (citations and quotations omitted). In *Merck*, defendant Sandoz argued that the invention was the result of "routine pharmaceutical development," but it entailed a freeze-drying process that was "very hard to predict." *Id.* at *8-9 ("[T]he skilled artisan must experiment with freeze-drying and cannot predict the outcome of the experiments."). There as here, the Defendants "cannot prove that [the claimed invention] was a predictable solution, and thus cannot prove obviousness through this approach." *Id.* at *9.

[0119] Defendants argue that the '855 Patent discloses ethanol as the recrystallization solvent for the preparation and isolation of armodafinil, such that a skilled artisan would not have to choose between a wide range of solvents to obtain Form I. [Hollingsworth 268:1-4; Lee 318:1-319:24.] This is clearly impermissible hindsight analysis, because the skilled artisan

would not have known of the existence of Form I, and could not have known a method to produce Form I with any solvent. [FOF 86, 87, 100.] It was only after the '570 Patent that a skilled artisan would know that Form I exists and would understand a method to recrystallize Form I from ethanol under slow cooling conditions. [JTX-1-32 at 27:37; FOF 86.] *See Glaxo Group*, 376 F.3d at 1348-49; *Pfizer*, 2012 WL 2951367, at *13; *Bone Care Int'l, L.L.C. v. Roxane Labs., Inc.*, No. 09-cv-285 (GMS), 2012 WL 2126896, at *40 (D. Del. June 11, 2012).

[0120] Nor can the Defendants rely on non-prior art experiments to bootstrap their obviousness argument. [Tr. 419:14-420:8.] To the contrary, it is imperative to consider whether the claimed invention "would have been obvious at the time the invention was made" to avoid the insidious attraction of hindsight. 35 U.S.C. §103(a) (2004) (emphasis added); *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 421 (2007); *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375 (Fed. Cir. 2011) ("Importantly, the great challenge of the obviousness judgment is proceeding without any hint of hindsight."); *Sanofi-Synthelabo*, 550 F.3d at 1088 ("Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation. The application of hindsight is inappropriate where the prior art does not suggest that this enantiomer could reasonably be expected to manifest the properties and advantages that were found for this particular dextrorotatory isomer.").

[0121] The evidence shows that the results of crystallization and polymorphism testing cannot be predicted. Indeed, the absence of predictability is the reason why crystallization experiments using a large number of variable conditions are conducted in the first place. [FOF 102.] For this reason, even if the general idea of using crystallization experiments were obvious to try, such unpredictable trial and error experimentation fails to render obvious Form I.

1. Trial and Error Experiments Do Not Prove Obviousness

[0122] "Obvious to try" is also not obvious when a skilled artisan would have to (1) "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," or (2) "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *see also Kubin*, 561 F.3d at 1359-60 (reaffirming the holdings in *O'Farrell* in view of *KSR*); *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (citing *O'Farrell*). For example, in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, the invention was not obvious, even if obvious to try, because "skilled artisans would not have encountered finite, small, or easily traversed options in developing a therapeutically effective, extended-release formulation." 676 F.3d 1063, 1073 (Fed. Cir. 2012) (emphasis added).

[0123] This holds true even where the technique used in the claimed invention is known in the art, but the experimental process and its results are complex or unpredictable and there is no reasonable expectation of success. *See, e.g.*, *Sanofi-Synthelabo*, 550 F.3d at 1088 (prior art did not suggest that claimed enantiomer would exhibit certain properties and advantages); *Sanofi-Synthelabo v. Apotex, Inc.*, 492 F. Supp. 2d 353, 391 (S.D.N.Y. 2007) ("The superiority of [the enantiomer] to [the racemic mixture]—which was only confirmed later—was clearly not obvious to the chemists at Sanofi."); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1378-80 (Fed. Cir. 2006) ("The court determined that nothing existed in the prior art that would make pursuing the enantiomer of [drug compound] an obvious choice, particularly in light of the unpredictability of the pharmaceutical properties of the enantiomers and the potential for

enantiomers to racemize in the body."); *Forest Labs., Inc. v. Ivax Pharm.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (holding that the claimed enantiomer was non-obvious where resolution of a racemate, while a known technique, is difficult and complex, the properties of enantiomers are not known until separated and tested, and the complexity of the technique did not permit a reasonable expectation of success). Thus, where the prior art provides only general guidance, it is error to find that "'obvious to try' proves obviousness." *Merck*, 2012 WL 266412, at *9-10.

[0124] The motivation on which Defendants rely was a general motivation to try to make new armodafinil crystal forms, and not directed at the later discovered Form I. Since the search for new crystal forms was entirely unpredictable, Defendants are proposing no more than exploring a general approach based on varying all parameters. *See, e.g.*, *O'Farrell*, 853 F.2d at 903; *Cyclobenzaprine*, 676 F.3d at 1073. Thus, Form I would have not have been obvious.

2. The Prior Art Did Not Suggest the Steps Necessary to Produce Form I or a Pharmaceutical Composition Consisting Essentially of Form I

[0125] "Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless . . . [the] skilled artisans would have had a reason to select the route that produced the claimed invention." *Cyclobenzaprine*, 676 F.3d at 1072. To the contrary, "[t]o render a claim obvious, prior art cannot be 'vague' and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution." *Unigene Labs., Inc. v. Apotex, Inc*., 655 F.3d 1352, 1361 (Fed. Cir. 2011) (citations and quotations omitted).

[0126] Thus, an invention is not obvious even if "obvious to try" when a field is "unreduced by direction of the prior art," and when prior art gives "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Id.* Further, "hindsight claims of obviousness" should be rejected when a defendant

is "merely throw[ing] metaphorical darts at a board" in hopes of arriving at a successful result, and "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Cyclobenzaprine*, 676 F.3d at 1070-71 (quoting *Kubin*, 561 F.3d at 1359 (quoting *O'Farrell*, 853 F.2d at 903)). For these reasons, the results of trial and error experimentation in an unpredictable field are not obvious.

[0127] Here, there was nothing to direct a skilled artisan to a route that would have produced the claimed invention. To the contrary, as discussed in section VI.C.2, *supra*, no prior art provided specific conditions to use for seeking new polymorphs of armodafinil and none necessarily produced material suitable for a pharmaceutical composition consisting essentially of Form I, as required by claims 6 and 9. Accordingly, for these additional reasons, Defendants failed to meet their burden to prove that these claims would have been obvious.

CEPHALON IS ENTITLED TO INJUNCTIVE RELIEF

[0128] "The court shall order the effective date of any [FDA] approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed" and may grant "injunctive relief . . . against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug." 35 U.S.C. §§ 271(e)(4)(A), (B).

[0129] Because the Defendants have stipulated that their proposed generic armodafinil ANDA products will infringe claims 6 and 9 of the '570 Patent, and because both of those claims are not invalid, the FDA is enjoined from approving Defendants' armodafinil ANDAs, and the Defendants are enjoined from commercially manufacturing, using, offering for sale, or selling their proposed armodafinil ANDA products, prior to the expiration of the '570 Patent, including any associated extensions and exclusivities.

[0130] Cephalon reserves arguments under 35 U.S.C. § 285, for costs, and for fees.

Respectfully submitted,

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Dated: October 17, 2012

CERTIFICATE OF SERVICE

I hereby certify that on the 17th day of October, 2012, I caused to be served a true and correct copy of **PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** by electronically filing same with the Clerk of Court using the CM/ECF system which will send electronic notification of such filing to the following counsel of record for Defendants, and the document was also served in the manner indicated below:

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